Attorney Docket No. **PATENT**
Confirmation No.

UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Stephen Shaugnessy et al.
Serial No. 09/491,982
Filed: January 27, 2000
For: OSTEOPOROSIS TREATMENT

Group Art Unit: 1646
Examiner: Mertz, Prema

Declaration Under 37 C.F.R. § 1.132

Stephen Shaughnessy states as follows:

1. I am the named inventor and applicant on the above application.

2. I reside at
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St. Catharines, Ontario
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3. My formal education includes:
- Honours B.Sc. Brock University, 1982
- Masters (Biochemistry), Brock University, 1985
- Ph.D. (Medical Sciences), McMaster University, 1992
- Post-Doctoral Fellow, Dept. of Medicine, McMaster University, 1992-94

4. I am currently an Associate Professor in the Dept. of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada.

5. I have approximately 11 years of postdoctoral research experience.

6. My research has focused on the study of bone.

7. I am a member of The American Society for Bone and Mineral Research.

8. I have many publications in the field of osteogenesis. I have received a new investigators award from the Heart and Stroke Foundation of Canada as well as a Premiers Research Excellence Award.

9. I am a co-inventor along with Richard Carl Austin of the subject matter claimed in the application entitled "Osteoporosis Treatment" which was filed in the United States Patent and Trademark Office on January 27, 2000. The invention provides a novel method for the treatment and/or alleviation of symptoms of clinical conditions, such as osteoporosis, in which the increased bone resorption or decreased bone formation is the underlying pathology, as described in the summary of the invention on page 3 of the application.

10. Our invention provides several surprising results. While osteoclast and osteoblast activities are complementary (i.e. have opposite effects) their activities are <u>not</u> balanced in the sense of a see-saw where, when one goes up, the other goes down. For example, there are several references that demonstrate that ovariectomization (similar to post-menopausal osteoporosis) results in an <u>increase in both</u> bone resorption and bone formation. A few of the references include:

    i. Wronski et al. Skeletal alterations in ovariectomized rats. Calcif Tissue Int (1985) 37:324-328
    ii. Wronski et al. Temporal relationship between bone loss and increased bone turnover in ovariectomized rats. Calcif Tissue Int. (1988) 43:179-183
    iii. Wronski et al. Histologic Evidence for osteopenia and increased bone turnover in ovariectomized rats. Bone (1986) 7:119-123.

11. It is clear from the evidence that some other agents simultaneously <u>inhibit both</u> osteoclast and osteoblast function. This further demonstrates that the assertion that "if one goes up, it is obvious that the other would go down" is a faulty conclusion. The references given below demonstrate that agents such as estrogen, bisphosphonates and calcitonin all simultaneously inhibit both bone formation and bone resorption. In

addition ref 5 demonstrates that an IL-1R antagonist inhibits bone resorption while having no effect on bone formation, further illustrating the surprising results of the present invention. The references include:

i. Wronski et al. Estrogen and Diphosphonate treatment provide long-term protection against osteopenia in ovariectomized Rats. J. Bone and Mineral Research. (1991) 6:387-394.

ii. Shen et al. Skeletal effects of calcitonin treatment and withdrawl in ovariectomized rats. Calcif Tissue Int (1996) 58:263-267

iii. Turner et al. Mechanism of action on cancellous bone balance in Tibiae of ovariectomized growing rats: Inhibition of indices of formation and Resorption. J Bone and Mineral Research (1993) 8:359-366

iv. Wronski et al. Endocrine and pharmacological suppressors of bone turnover protect against osteopenia in ovariectomized rats. Endocrinology (1989) 125:810-816

v. Kimble et al. Interleukin-1 receptor antagonists decreases bone loss and bone resorption in ovariectomized rats. J Clin Invest. (1994) 93:1959-1967.

12. It is further clearly apparent from the evidence that some agents can simultaneously stimulate both osteoclast and osteoblast function. The following reference shows that PTH increases bone formation while causing a small transient increase in bone resorption (ie. it certainly does not inhibit bone resorption):

i. Meng et al. Temporal expression of the anabolic action of PTH in cancellous bone of ovariectomized rats.(1996) 11:421-429

13. The significant effects seen with the products and methods of the present invention were further surprising due to the commonly held assumption that there is cytokine redundancy whereby the effect of a specific cytokine can be compensated by others in its absence. In the present invention, we did not know at the time what to expect if we antagonized IL-11 function in vivo, since numerous hormones, cytokines and growth factors were known to either directly or indirectly stimulate osteoclast formation and

activity. These include PTH, Vitamin D3, PGE2, IL-1, IL-6, TNF, FGF, TGF-ß, and IL-17 just to mention a few. Thus it was quite possible that we would see no effect when IL-11 activity was neutralized either because the ability of IL-11 to stimulate bone resorption in vivo was relatively small compared to these other cytokines, or because once its activity was neutralized, other cytokines would through cytokine redundancy, make up for the loss. Only after conducting the experiments in the application did we know neither of these possibilities was the case. Furthermore, we also made the surprising finding that by targeting IL-11, we could enhance the process of bone formation in OVX mice. This suggests that IL-11 not only acts to promote the process of osteoclast-mediated bone resorption but that it also acts in vivo as an inhibitor of osteoblast-mediated bone formation - a finding which was completely unexpected. In the present invention, we were able to significantly inhibit the process of bone resorption in an animal model of postmenopausal bone loss without worrying about simultaneously inhibiting the process of bone formation.

The following reference demonstrates that IL-11 action is redundant when it comes to its effects on hematopoiesis. Ie. while administration of IL-11 is known to cause enhanced white blood cell and platelet counts, "knocking out" the IL-11 receptor in mice does NOT result in a decrease in either white blood cell or platelet numbers because other members of the IL-11 family can compensate for the loss in IL-11 activity:

1. Nandurkar H et al. The role of IL-11 in Hematopoiesis as revealed by a targeted mutation of its receptor. Stem Cells 1998, 16:53-65

Thus, I believe it could not have been obvious that an anti-IL-11 antagonist would show beneficial effects.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued hereon.

Dr. S. Shaughnessy

Date: March 11/05